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Neural correlates of executive function and working memory in the 'at-risk mental state'

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Background
People with prodromal symptoms have a very high risk of developing psychosis.

Aims
To use functional magnetic resonance imaging to examine the neurocognitive basis of this vulnerability.

Method
Cross-sectional comparison of regional activation in individuals with an 'at-risk mental state' (at-risk group: *n*=17), patients with first-episode schizophreniform psychosis (psychosis group: *n*=10) and healthy volunteers (controls: *n*=15) during an overt verbal fluency task and an N-Back working memory task.

Results
A similar pattern of between-group differences in activation was evident across both tasks. Activation in the at-risk group was intermediate relative to that in controls and the psychosis group in the inferior frontal and anterior cingulate cortex during verbal fluency, and in the inferior frontal, dorsolateral prefrontal and parietal cortex during the N-Back task.

Conclusions
The at-risk mental state is associated with abnormalities of regional brain function that are qualitatively similar, but less severe, to those in patients who have recently presented with psychosis.

Declaration of interest
None. Funding detailed in Acknowledgements.

People with prodromal symptoms of psychosis have a 25–40% risk of developing a psychotic disorder in the next 12 months[1,2] and thus have an 'at-risk mental state'. Neuropsychological studies indicate people with an at-risk mental state show impairments in executive and memory functions with performance often intermediate between that in patients with schizophrenia and controls,[3] with working memory performance predicting the onset of psychosis.[4] Structural magnetic resonance imaging (MRI) studies suggest that the at-risk mental state is associated with reduced grey-matter volume in regions that are also abnormal in schizophrenia,[5] and a recent functional MRI study reported differential prefrontal activation in individuals with an at-risk mental state relative to controls and patients with schizophrenia during a visual oddball paradigm.[6] Taken together, these findings suggest that individuals with an at-risk mental state display neurocognitive abnormalities that are qualitatively similar to, but less severe than, those seen in schizophrenia. We tested this hypothesis using functional MRI in conjunction with classical tasks of executive function and working memory.

Methods

Participants

At-risk mental state (at-risk) group (*n*=17)

Individuals meeting Personal Assessment and Crisis Evaluation[7] (PACE) criteria for an at-risk mental state were recruited from Outreach and Support in South London (OASIS).[8] The diagnosis was based on assessment by two experienced clinicians using the comprehensive assessment for the at-risk mental state,[2] and a consensus meeting with the clinical team. None of the participants had ever received antipsychotic medication. Briefly, an individual meets PACE criteria for an at-risk mental state if they display one or more of the following: 'attenuated' positive symptoms; frank psychotic symptoms that last less than 1 week and resolve without treatment; a recent decline in function coupled with either schizotypal personality disorder or a first-degree relative with psychosis. The individuals recruited were representative of the local population of people presenting with an at-risk mental state in terms of age, gender, ethnicity, and duration and intensity of symptoms.[8]

First-episode (psychosis) group (*n*=10)

Participants were patients who had presented with a first episode of psychosis to Lambeth Early Onset Services. All met ICD–10[9] criteria for a schizophreniform psychosis at the time of scanning and subsequently met Operational Criteria Checklist (OPCRIT)[10] criteria for schizophrenia when reassessed 12 months after first presentation. Three patients were medication naïve. Seven had been treated with either oral risperidone or quetiapine for a mean of 10 days (95% CI 4.7–16.3) at mean doses of 1.7 mg and 63.75 mg respectively. Patients were scanned as soon after presentation as was practicable, and all but one of the patients scanned within 2 weeks of presentation.

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Control group (*n*=15)

Healthy volunteers were recruited via advertisements in the local media.

All individuals lived in the same borough of London as the clinical participants (Lambeth), were native speakers of English and were right-handed.

Individuals were excluded if there was a history of neurological disorder or they met DSM–IV[11] criteria for a substance misuse disorder. General intellectual function was estimated in all participants using the National Adult Reading Test.[12] The severity of symptoms in the clinical groups was assessed with the Positive and Negative Syndrome Scale (PANSS)[13] on the day

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of scanning. Additionally, individuals were excluded from the analysis after data collection if they were unable to perform the cognitive tasks during image acquisition as detailed below. For the at-risk group, 19 participants underwent functional MRI, with 2 being excluded due to not performing the task resulting in n=17; for the psychosis group, 1 participant was excluded and similarly for the control group leaving data being reported for n=10 and n=15 respectively.

There were no significant group differences in socio-demographic variables or IQ. Both positive and general PANSS scores were higher in the psychosis group than in the at-risk group, but these differences were not significant (Table 1).

Image acquisition

Images were acquired on a 1.5 Tesla Signa (GE) system at the Maudsley Hospital, London. T_2*-weighted images were acquired with a repetition time (TR) of 2 s, 38 x 3 mm slices, with a 0.3 mm gap in 14 axial planes. During verbal fluency a gradient-echo sequence (TR=4000 ms, echo time (TE)=40 ms) was used with the acquisition of each volume compressed into the first 1250 ms of the repetition time, creating a 2750 ms window in which participants could articulate a response in the absence of scanner noise.[14] The other tasks (which did not involve speech) were studied using TR=2000 ms and TE=40 ms. To facilitate anatomical localisation of activation, a high resolution inversion recovery image data-set was also acquired, with 3 mm contiguous slices and an in plane resolution of 3 mm (TR=1600 ms, inversion time (TI)=180 ms, TE=80 ms).

Cognitive tasks

N-Back

In all conditions participants were presented with a series of letters which they viewed using a prismatic mirror. The interstimulus interval was 2 s. During the baseline (0-Back) condition, individuals were required to move a joystick to the left when the letter 'X' appeared. During the 1-Back and 2-Back conditions, participants were required to press a button on the joystick with their right index finger if the currently presented letter was the same as that presented one or two trials beforehand respectively. The three conditions were presented in 10 alternating 30-s blocks matched for the number of target letters per block (i.e. two or three), in pseudorandom order. Reaction time and the accuracy of the responses were recorded online.

Overt verbal fluency

Participants were required to overtly articulate a word beginning with a visually presented letter. The stimuli, each subtending an angle of 5, were presented visually on a black screen, viewed through a mirror. Cognitive load was modulated with two levels of task difficulty, 'easy' and 'hard' conditions, which involved letters that differed with respect to the ease with which volunteers can usually generate words beginning with them. The 'easy' condition involved the letters L, T, C, P, S; the 'hard' condition: O, N, E, F, G.[14] Incorrect responses were defined as words that were proper names, repetitions or grammatical variations of the previous word, and 'pass' responses. Letters were presented in 28-s blocks of seven stimuli at 4-s intervals. The control condition of word repetition comprised 28 s blocks of 7 presentations of the word 'rest' at 4 s intervals, which participants were required to read aloud. Five blocks of each condition (hard/easy/repetition) were presented in random order.

Verbal responses were recorded via an MRI compatible microphone on Cool Edit 2000. To ensure that participants heard their responses clearly, their speech was transmitted by an MRI compatible microphone, amplified by a computer sound card and relayed back through an acoustic MRI sound system (Ward Ray, Hampton Court, UK), and noise insulated, stereo headphones at a volume of 91 plus or minus 2 dB.

Author: Please clarify which platform was used, Mac, Windows? (Column 2) (AQ5)

Image processing and analysis

The data were realigned[15] then smoothed using a Gaussian filter (full width half maximum 7.2 mm). Responses to the experimental paradigms were detected by convolving each component of the design with each of two gamma variate functions (peak responses at 4 and 8 s respectively). The best fit between the weighted sum of these convolutions and the time series at each voxel was computed using the constrained blood oxygen level dependent (BOLD) effect model.[16] A goodness of fit statistic comprising the ratio of the sum of squares of deviations from the mean image intensity (over the whole time series) divided by the sum of squares of deviations due to the residuals (SSQratio) was then computed at each voxel.

The data were then permuted by a wavelet-based method[17] to calculate the null distribution of SSQratios under the assumption of no experimentally determined response. This was used to calculate the critical value of SSQratio needed to threshold the maps at a type I error rate of <1. The detection of activated voxels was then extended from voxel to cluster level.[18] To minimise the potential confounding effects of between-group and between-condition variation in task performance, in the analysis of data from the verbal fluency and N-Back tasks the BOLD response in each person was modelled using only trials associated with correct responses.

In addition to the SSQratio, the size of the BOLD response to each experimental condition was computed for each individual at each voxel as a percentage of the mean resting image intensity level. In order to calculate the BOLD effect size, the difference between the maximum and minimum values of the fitted model for each condition was expressed as a percentage of the mean image intensity level over the whole time series.

Table 1 Age, IQ, gender and psychopathology ratings across groups

Variable	Controls (n=15)	At-risk group (n=17)	Psychosis group (n=10)
Age, years: mean (s.d.)	25.4 (4.9)	24.2 (4.1)	25.5 (5.9)
Gender, male:female	11:4	12:5	7:3
NART IQ: mean (s.d.)	111.2 (7.2)	102.9 (11.9)	103.6 (9.2)
PANSS total: mean (s.d.)	N/A	51. 9 (12.7)	58.1 (9.5)
PANSS positive: mean (s.d.)	N/A	11.7 (3.4)	18.5 (4.6)
PANSS negative: mean (s.d.)	N/A	10.6 (4.1)	10.0 (2.3)
PANSS general: mean (s.d.)	N/A	20.9 (9.2)	29.6 (5.9)

NART, National Adult Reading Test; PANSS, Positive and Negative Syndrome Scale.

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The SSQratio maps for each individual were transformed into the standard space of Talairach and Tournoux[19] using a two-stage warping procedure.[20] Group activation maps were computed by determining the median SSQratio at each voxel (across all individuals) in the observed and permuted data maps. The distribution of median SSQratios from the permuted data was used to derive the null distribution of SSQratios and the critical SSQ ration to threshold group activation maps at a cluster level threshold of <1 expected type I error cluster per brain.

Comparisons of responses between groups or experimental conditions was performed by fitting the data at each intraceberal voxel at which all participants had non-zero data using a linear model of the type:

$$Y = a + bX + e$$

Where Y is the vector of BOLD effect sizes for each individual, X is the contrast matrix for the particular intercondition/group contrasts required, a is the mean effect across all individuals in the various conditions/groups, b is the computed group/condition difference and e is a vector of residual errors. The model was fitted by minimising the sum of absolute deviations rather than the sums of squares to reduce outlier effects. The null distribution of b was computed by permuting data between conditions/groups (assuming the null hypothesis of no effect of experimental condition or group membership) and refitting the above model.

In order to examine the data for a linear trend in activation across groups (controls, at-risk and psychosis) we carried out an orthogonal polynomial trend analysis in which the linear trend was coded as -1, 0, 1 (controls, at-risk and psychosis) and the orthogonal polynomial trend as -1, 2 and -1. Our hypothesis was that the linear trend would be significant but the quadratic trend would not be (i.e. there would be a linear trend but no significant departure from linearity). This would indicate that the order of responses would be controls > at-risk > psychosis or psychosis > at-risk > controls. This analysis was carried out using the effect size (beta) maps (which represented percentage changes in BOLD response) for each individual in each group after these had been transformed into in standard space.

Voxel and cluster level maps of voxels and clusters showing significant linear and quadratic effects were computed using permutation testing as described above. The threshold for cluster level analysis was chosen to give <1 false activated cluster per brain.

The method of analysis we employed (XBAM) uses median statistics to control outlier effects and permutation rather than normal theory-based inference. The main test statistic is computed by standardising for individual differences in residual noise before embarking on second level, multiperson testing using robust permutation-based methods. Approaches using a mixed effects analysis, and permutation-based and cluster level inference appear to be more valid than analyses involving simple random effects and voxel level inference.[21]

Results

Task performance

There were no significant group differences in mean reaction time (P=0.44), and no differences in the number of errors during the 1- and 2-Back conditions (P=0.49).

There were no significant group differences in mean reaction time (P=0.81). There was a group difference in the proportion of movements made to the right (F=4.05, d.f. χ^2=2, P=0.028): controls made more such movements than the at-risk group, with the psychosis group intermediate between them.

There were no group differences in the number of errors produced during either the 'easy' (P=0.45) or 'hard' versions of the task (0.82).

Author: Should this be P=0.82? (Column 2) (AQ6)

Regional activation

Within-group activation (voxel $P<0.05$, cluster $P<0.01$)

1-Back. In the control group, there was activation in the left inferior frontal gyrus and the posterior parietal cortex bilaterally. In the at-risk group, activation was evident in the inferior and middle frontal gyri bilaterally, the left inferior parietal and right inferior temporal cortex, and the left fusiform gyrus. The psychosis group displayed activation in the middle and superior frontal gyri bilaterally, the right inferior frontal gyrus, the left insula, the medial parietal cortex bilaterally, the right middle temporal gyrus and thalamus.

2-Back. In the control group there was activation in the left precentral and medial frontal gyrus, the right inferior frontal gryus, and the left posterior and right medial parietal cortex. In the at-risk group, activation was evident in the right inferior frontal and the left middle frontal gyrus, and in the right posterior cortex and left precuneus. The psychosis group displayed activation in the inferior and middle frontal gyri bilaterally, the middle temporal gyrus bilaterally, and in the left thalamus and caudate

Between-group differences in activation (voxel $P<0.05$, cluster $P<0.01$)

1-Back. There was differential activation across the three groups in the left inferior parietal lobule and the right angular gyrus. In both these areas the at-risk group showed less activation than controls but more activation than the psychosis group (*post hoc* t-tests, $P<0.05$) (Fig. 1 and Table 2).

2-Back. Differential activation across the three groups was evident in the right insula and left inferior frontal gyrus, the right inferior parietal lobule, the left precuneus and right medial/superior frontal gyrus. In each of these areas the at-risk group showed less activation than controls but more activation than the psychosis group (*post hoc* t-tests, $P<0.05$) (Fig. 1 and Table 3).

Verbal fluency

Within-group activation (voxel $P<0.05$, cluster $P<0.01$).

'Easy' condition. Controls showed activation in the left inferior and superior frontal gyri, the at-risk group activated the left inferior frontal and left fusiform gyri, right insula, and left superior frontal gyrus, and the psychosis group activated the left precentral gyrus, right insula, and the left inferior parietal and fusiform cortex.

'Hard' condition. Controls displayed activation in the left inferior frontal gyrus and inferior parietal lobule, and the right posterior cerebellar cortex. The at-risk group activated the left inferior frontal gyrus, the left superior frontal gyrus, while the psychosis group activated the left precentral gyrus and insula, and the right inferior frontal gyrus, insula and anterior cingulate gyrus.

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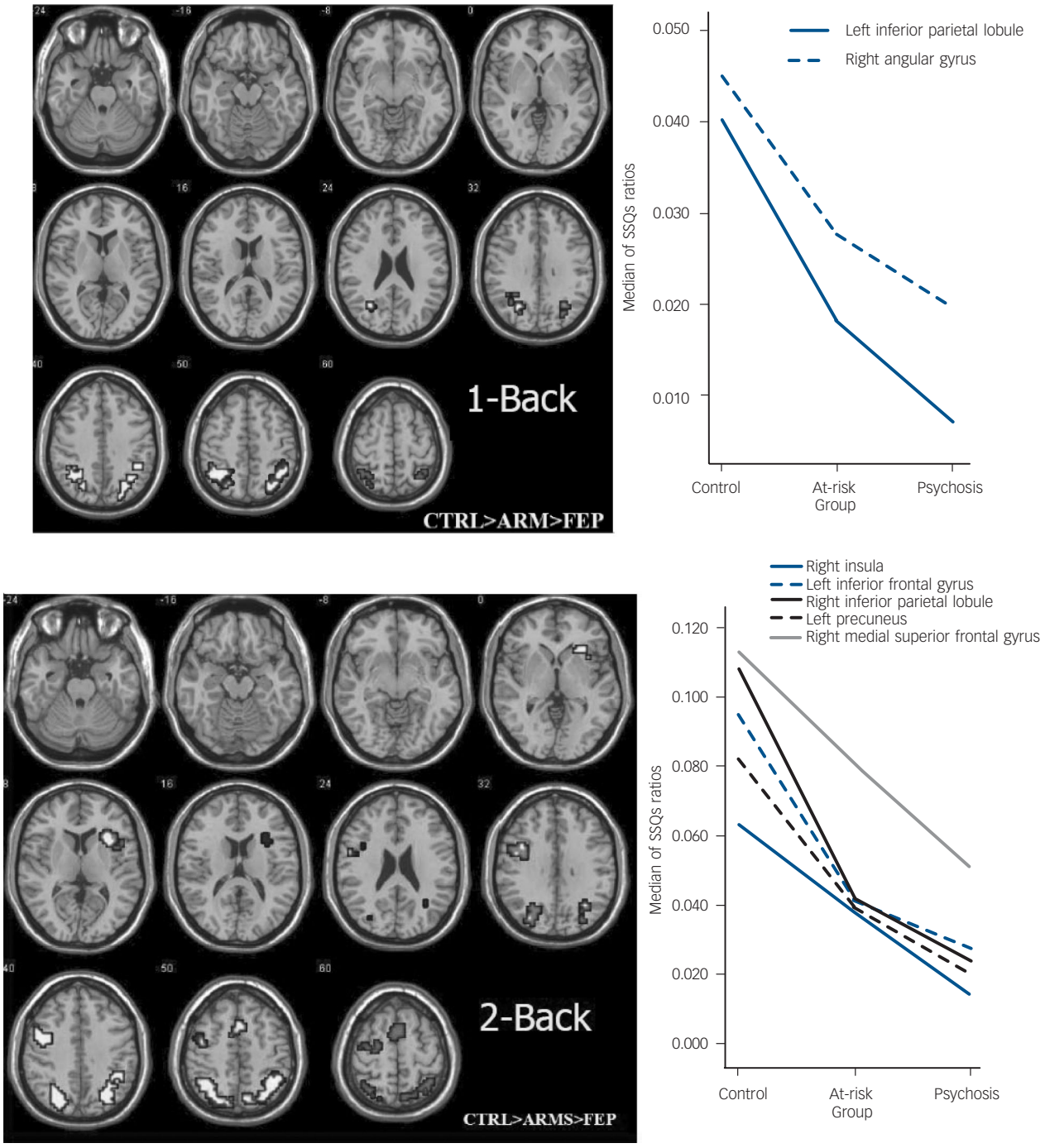

Fig. 1 Group differences in cluster activation during the 1-Back and 2-Back conditions of the N-Back task. For the 1-Back condition, activation was greatest in controls, weakest in the psychosis group and intermediate in the at-risk group in the left inferior parietal lobule and in the right angular gyrus. Differential activation during the 2-Back condition was greatest in controls, weakest in the psychosis group and intermediate in the at-risk group in the lateral prefrontal, insular and parietal cortex, and in the precuneus, The left side of the brain is shown on the left of the figure (voxel $P<0.05$, cluster $P<0.01$). SSQRs, sum of squares of deviations due to the residuals.

Between-group differences in activation (voxel $P<0.05$, cluster $P<0.01$)

'Easy' condition. There was differential activation across the three groups in a region which included both the opercular and dorsal parts of the left inferior frontal gyrus (Fig. 2 and Table 4). The at-risk group showed less activation in this region than controls but more activation than the psychosis group (*post hoc* *t*-tests, $P<0.05$).

'Hard' condition. Differential activation across the three groups was evident in a region which extended superiorly from the dorsal part of inferior frontal gyrus to adjacent middle frontal and precentral gyri (Fig. 3 and Table 5). In this region, the at-risk group showed less activation than the controls but greater activation than the psychosis group (*post hoc* *t*-tests, $P<0.05$).

The reverse pattern of differential activation was evident in a more ventral region focused on the left anterior insula. In this region activation was again intermediate in the at-risk group,

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Table 2 1-Back task between-group differences in activation: controls > at-risk > psychosis

Talairach and Tournoux coordinates (*x, y, z*)	Anatomical region	Brodmann area	Cluster size (number of voxels)
32, –59, 17	Posterior part of right middle temporal gyrus	39	37
−40, −48, 37	Left inferior parietal lobule	40	31
29, −63, 31	Right precuneus	7	16
40, −48, 42	Right inferior parietal lobule	40	9
−22, −59, 26	Left precuneus	31	7

but was greatest in the psychosis group and weakest in the controls (Fig. 3 and Table 6). *Post hoc* pairwise comparisons confirmed that in this region the at-risk group showed greater activation than controls with a trend for less activation than the psychosis group (*t*-tests, $P<0.05$).

Effects of medication

Within the psychosis group (the only group which included participants who had received antipsychotic medication), there was no significant correlation (voxel $P<0.05$, cluster $P<0.01$) between activation in the regions that were differentially engaged across groups during each task and either the daily or cumulative dose (in chlorpromazine equivalents) of antipsychotic treatment, or the duration of antipsychotic treatment.

Discussion

The present study used functional MRI to study the neural substrate of executive functions and working memory in individuals with an at-risk mental state. The N-Back task engages verbal working memory and requires the suppression of responses to currently presented stimuli. Verbal fluency entails the intrinsic generation of a verbal response, suppression of inappropriate responses and the holding of information about previous responses online.

In line with our hypothesis, there was a consistent pattern of differential activation across the groups for both tasks: during the N-Back and verbal fluency paradigms, the level of regional activation in the at-risk group was intermediate between that in the psychosis group and controls. This is the first study to demonstrate statistically intermediate patterns of activation in an at-risk group, compared with controls and participants with psychosis. These differences were evident in brain regions that are normally activated during these paradigms in volunteers: the prefrontal and parietal cortex during the N-Back task, and the prefrontal and anterior cingulate cortex during verbal fluency.[22–28] The differential activation was not attributable to impairments in task performance, as there were no significant differences in the speed or accuracy of responses across groups, and the analysis selectively modelled the BOLD response to those trials associated with correct responses. The lack of difference in behavioural performance allows the interpretation of activations to proceed knowing that the psychological task is being carried to an equal level by all participants and hence, any remaining difference in activation is likely to be due to the disorder of interest, rather than a non-specific correlate of poor performance. The lack of behavioural difference is due both to excluding individuals who perform the task very badly from the analysis and by the study being powered to detect physiological changes, rather than neuropsychological differences, between the groups.

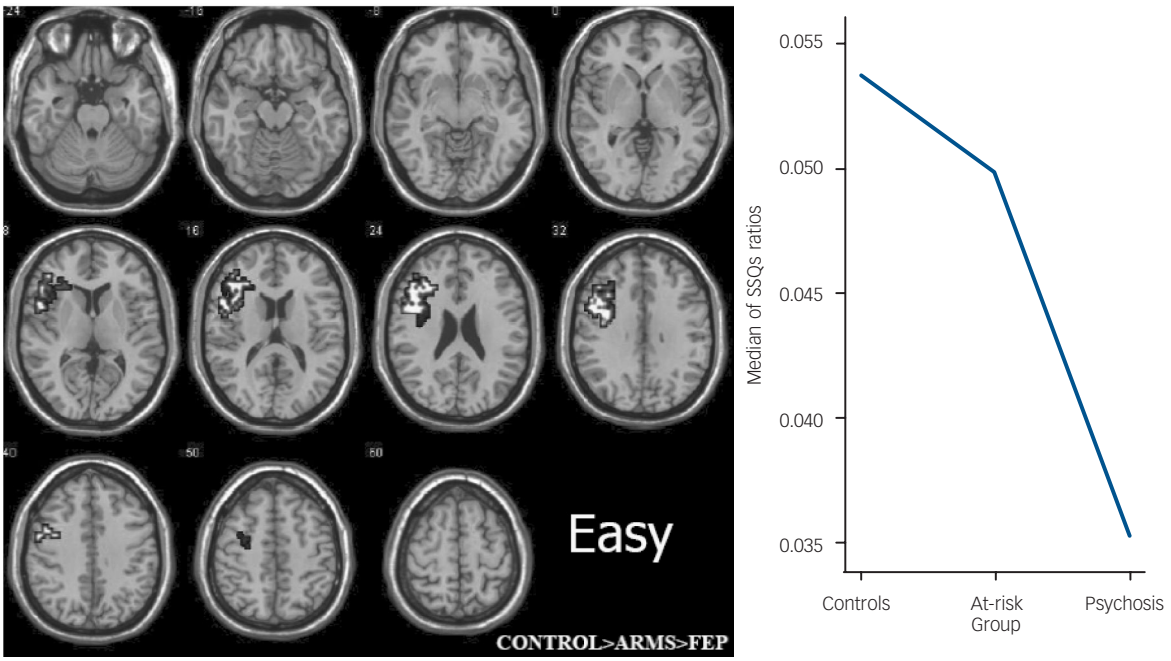

Fig. 2 Group differences in left inferior frontal cluster activation during 'easy' verbal fluency. The at-risk group showed greater activation than the psychosis group but less than that in controls. The left side of the brain is shown on the left of the figure (voxel $P<0.05$, cluster $P<0.01$). SSQRs, sum of squares of deviations due to the residuals.

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Table 3 2-Back task between-group differences in activation: controls > at-risk > psychosis

Talairach and Tournoux coordinates (*x, y, z*)	Anatomical region	Brodmann area	Cluster size (number of voxels)
40, −44, 42	Right inferior parietal lobule	40	38
−22, −70, 42	Left precuneus	7	35
−40, −41, 37	Left inferior parietal lobule	40	31
29, −59, 31	Right precuneus	7	29
−18, −74, 17	Left calcarine sulcus	17	26
32, 22, −2	Right post insula/claustrum		22
−40, 11, 26	Left inferior frontal gyrus	44	19
4, 11, 48	Medial part right superior frontal gyrus	6	18
36, −56, 48	Right superior parietal lobule	7	15
0, 15, 42	Anterior cingulate	32	12
−22, −4, 48	Left superior frontal gyrus	6	12

Table 4 Controls < at-risk < psychosis: 'easy' verbal fluency between-group differences in activation

Talairach and Tournoux coordinates (*x, y, z*)	Anatomical region	Brodmann area	Cluster size (number of voxels)
−36, 30, 15	Left inferior frontal gyrus.(anterior portion)	45	36
−40, 7, 20	Left inferior frontal gyrus (dorsal portion)	44	34
−47, 11, 9	Left inferior frontal gyrus (frontal operculum)	44	26

Table 5 Controls > at-risk > psychosis: 'hard' verbal fluency between-group differences in activation

Talairach and Tournoux coordinates (*x, y, z*)	Anatomical region	Brodmann area	Cluster size (number of voxels)
−43, 11, 15	Left inferior Frontal gyrus (frontal operculum).	44	18

Table 6 Psychosis > at-risk > controls: 'hard' verbal fluency between-group differences in activation

Talairach and Tournoux coordinates (*x, y, z*)	Anatomical region	Brodmann area	Cluster size (number of voxels)
−32, 15, −2	Left anterior insula	47	24

Similarly, the findings are unlikely to be related to effects of antipsychotic medication as both the at-risk group and controls were medication naïve, and in the psychosis group there was no relationship between medication exposure and activation in the regions that were differentially engaged across groups. Further, when quadratic trend analysis was carried out, there were no significant clusters activated differentially across the groups: again, this indicates that there was a predominantly linear relationship in activation across the groups on all tasks.

The brain regions where we observed differential activation in the at-risk group correspond to those that have previously been reported as sites of abnormal activation in functional imaging studies of schizophrenia. Thus, patients with schiziophrenia show reduced activation in the prefrontal and parietal cortex during the N-Back task,[24] in the parietal cortex during random movement generation,[29] and in the left prefrontal cortex during verbal fluency,[30] There has only been one previous functional imaging study involving participants with an at-risk mental state. This reported differential prefrontal activation during a visual oddball paradigm in an at-risk group relative to controls and patients with schizophrenia.[6]

During the 1-Back condition of the N-Back task, the at-risk group showed attenuated activation in the parietal cortex relative to controls. These differences became more extensive during the more demanding 2-Back condition, and were accompanied by additional reductions in prefrontal activation. Nevertheless, the magnitude of activation in the at-risk group remained intermediate to that in the control and psychosis groups when the task demands were increased. Similarly, although during 'hard' verbal fluency the pattern of activation differences in the insula was reversed (discussed further below), the magnitude of activation in the at-risk group remained intermediate relative to that in the other groups, as during the 'easy' version of the task, and did not more closely resemble that in the psychosis group.

During 'hard' verbal fluency, engagement of the left insula was greatest in the psychosis group, intermediate in the at-risk group and weakest in controls. In the dorsal part of the left inferior frontal gyrus the opposite applied, with greatest activation in controls and least in the psychosis group. Relatively greater engagement of the insula in the psychosis group in the context of increased demands on controlled word retrieval[31] and selection among competing words[32] might reflect a compensatory response in the group in whom processing was most compromised and who showed the weakest engagement of the inferior frontal gyrus.

The overall pattern of the findings is consistent with data from neuropsychological studies of the at-risk mental state. These indicate that individuals who are at risk display impairments on tasks of executive functions and memory (including N-Back and

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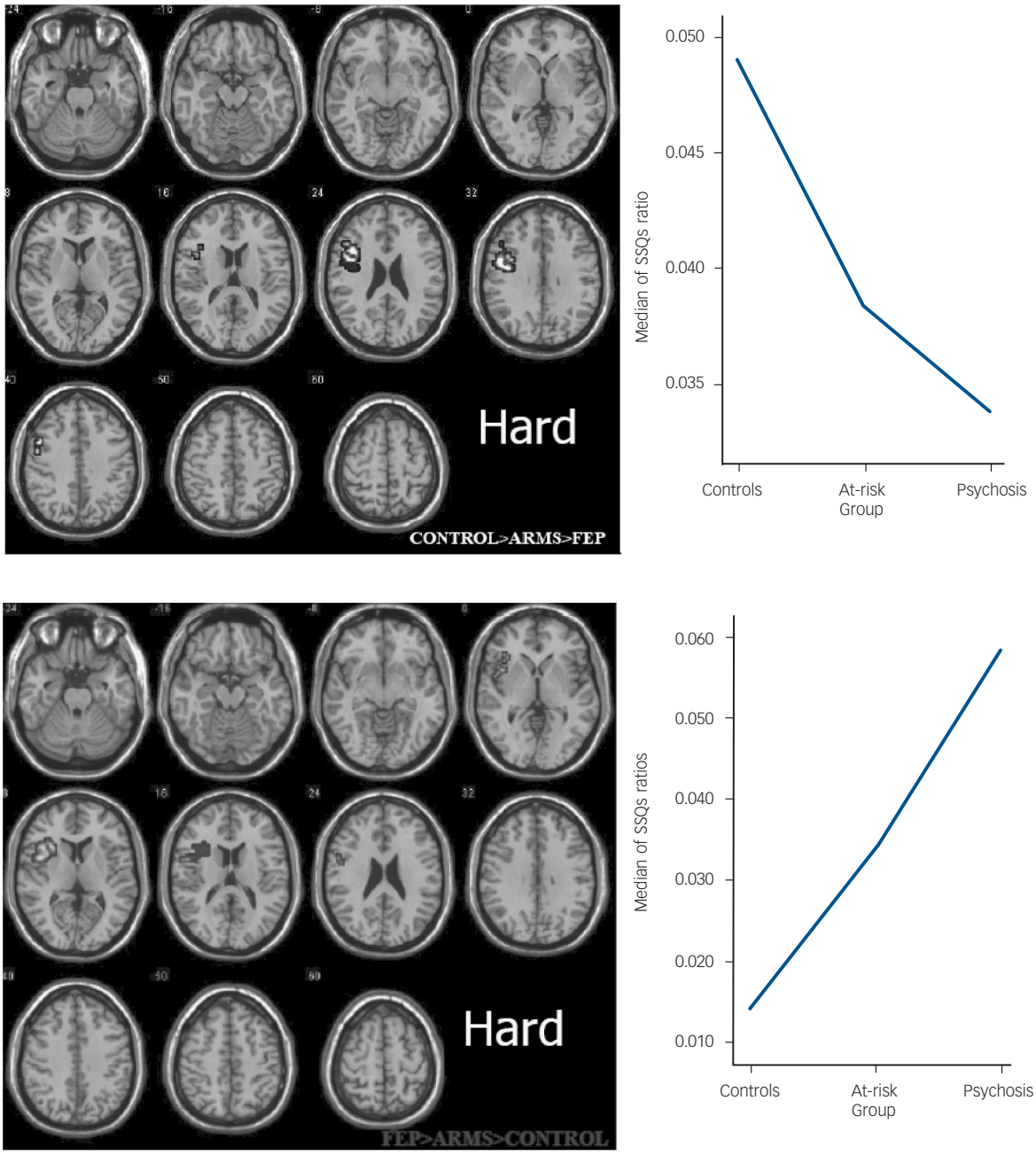

Fig. 3 Group differences in cluster activation during 'hard' verbal fluency. When the task demands were high, there was differential engagement of dorsolateral prefrontal cortex activation was greatest in the control group, weakest in the psychosis group, and intermediate in the at-risk group. However, on the same version of the task, there was differential engagement of the left anterior insula. When task demands were high activation in this region was greatest in the psychosis group, weakest in the controls and intermediate in the at-risk group. The left side of the brain is shown on the left of the figure (voxel $P<0.05$, cluster $P<0.01$). SSQRs, sum of squares of deviations due to the residuals.

verbal fluency) that are qualitatively similar, but less severe, than those evident in patients with schizophrenia.[33–37] Similarly, structural MRI studies suggest that the at-risk mental state is associated with reductions in grey-matter volume in similar regions that show volume reductions in schizophrenia, including the inferior frontal, cingulate and temporal cortex.[5] (Borgwardts *et al*, 2007).

As the at-risk group had a high risk of developing a psychotic disorder but did not have psychosis, the functional abnormalities they displayed can be seen as a correlate of their increased vulnerability to psychosis. It is unlikely that the findings reflected the erroneous inclusion of individuals who already had psychosis, or who were already progressing towards schizophrenia, as inclusion required detailed assessment by at least two clinicians experienced in the management of the at-risk mental state. In addition, participants were closely monitored for signs of frank psychosis subsequent to scanning.

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Limitations of the study

This study reports cross-sectional data on individuals at-risk, with psychosis and controls. As noted above, the findings in the at-risk group may be a correlate of their increased vulnerability to psychosis. However, to determine this formally will require a

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longitudinal study: a study informed by the findings presented here and in particular whether the pattern and degree of activation during executive and working memory tasks predict transition to psychosis in a clinical high-risk group.

Conclusions

The at-risk mental state is associated with abnormalities of regional brain function that are qualitatively similar but less severe than those seen in patients who have just developed schizophrenia. These may underlie the impairments in executive function and working memory that are evident in this group and can be seen as correlates of their increased vulnerability to psychosis.

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